

# **Three-generation familial risks in prostate cancer with a special focus on the early onset patients and their maternal and paternal relatives.**

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## **ABSTRACT**

**Background:** Swedish nationwide family and cancer data extend through three generations providing a unique chance for study of familial cancer in PC between first-degree relatives (FDR) and second-degree relatives (SDR). It also enables a test for the usefulness of maternal family information.

**Methods:** Familial relative risks (standardized incidence ratios, SIRs) for PC were calculated for young men in generation 3 when their brothers, fathers, uncles and grandparents were diagnosed with PC (they were probands).

Results: Familial SIRs for two affected brothers were 4.0 but when additionally a SDR (uncle or grandfather) was affected SIR reached 10.3. When a father was the proband, SIR was 3.1 but when additionally a SDR was affected SIR reached 4.7, and risk increased up to 11.6 with increasing numbers of affected SDRs. Importantly, affected SDRs were more numerous than FDRs. When a maternal or paternal grandfather was the only proband SIR for both was about 1.6. Both maternal and paternal uncles transmitted a risk of 1.6, and when two uncles were affected SIR climbed to about 2.0. The highest familial risk of 27 was found for affected brothers with a father and 2 SDRs diagnosed with PC.

Conclusions: The results showed that for the young patients in generation 3 the richest sources of familial probands were SDRs. The uncles belong to the generation of fathers, and they are likely to be more numerous than grandparents. Maternal and paternal SDRs are equally informative for genetic counseling and both parental lineages should be used as they provide equal familial information about the risks of PC.

## INTRODUCTION

Prostate cancer (PC) shows the highest heritability of all cancers in twin studies and the largest proportion of familial cases compared to other cancers in two-generation family studies (1-3). However the putative predisposition genes for PC were elusive at the time when major germline variants for colorectal and breast cancers were already known (4). The early method of choice to identify germline variants underlying familial clusters was based on the linkage design which was conducted in families presenting with the same cancer in several affected family members (4). The method attempted to identify small genetic segments that were shared by the affected family members but for PC it was not successful because of the assume complex genetic background (5). Instead, large case-control studies have been able to establish *BRCA2*, *HOXB13*, *BRCA1*, *CHEK2*, *PALB2*, *PMS2* and *ATM* as some of the most common predisposition genes for PC and newer studies are identifying further candidates (6-10). In a recent UK Biobank-based study significant association with PC were found for *HOXB13* T, odds ratio 4.4 and for *BRCA2*, *CHEK2* and *ATM*, odds ratios between 2.0 and 2.3 (11). The estimates of the combined contribution of the known pathogenic germline variants on PC vary widely from 4 or 5% in localized PC to 7.3% in familial PC to 12-16% in metastatic PC (12). In addition to the above 'high-risk' variants, low-penetrance variants contribute to familial risk of PC when a large number of risk allele are clustered in families (13-15). Many of the listed gene variants are also known to predispose to other cancers, for example *BRCA1* and *BRCA2* are the main breast cancer predisposition genes. Familial aggregation between PC and breast cancer is well known and most likely due to shared germline predisposition (11, 16). Genetic testing of PC patients may be recommended for patients with high familial risk undergoing genetic counseling (6, 12)

Almost all family studies on PC, and cancer in general, have been conducted among two-generation families because of data availability and expected highest risks between first-degree relatives (FDR). The exceptions have been the genealogic databases from Iceland and Utah with

data over many generations (17-19). A PC study from the Utah Population Database could demonstrate familial aggregation through 5 generations (20). The demographic changes in PC have been massive since the introduction of prostate specific antigen (PSA) screening in the 1990s: case numbers increased and ever younger patients were diagnosed (21). Previous family studies have not had statistical power to cope with the young patients in an era of decreasing family sizes. When a family's only son is diagnosed with PC, it will be a chance concordance if his father is also affected, unless they have high genetic risk. Then second-degree relatives (SDRs), uncles and grandparents are the most likely source for relevant information for genetic counseling but reliable data on the risks in second-degree relatives would be needed (20).

We apply here updated family data of Sweden covering essentially a century with cancers from a national high-quality cancer registry (22). The special features of these data are complete family structures and their cancer data on 16 million individuals. We use this resource by focusing on PCs in the early-onset cancer in generation 3, depending on proband PCs among FDRs and SDRs. We show, as expected, that familial risks are highest between FDRs but large numbers of PCs are diagnosed among SDR covering maternal and paternal relatives who would provide indispensable risk data for early-onset, high-risk patients.

## METHODS

The analyzed dataset originates from the latest update of the Swedish Cancer Registry (covering period 1958- 2021), linked with the Multigeneration Register, containing links to parents for individuals born after 1931. All family and cancer linkages were done through the unique personal identification number. Demographic details of PC in Sweden were obtained from the NORDCAN database (<https://nordcan.iarc.fr/en/dataviz>).

The study covered three generations, generation 1 born before 1932, generation 2 born from 1932 onwards and generation 3 children of parents from generation 2 (**Supplementary Table 1**). Siblings could be identified in generations 2 and 3 through common parents. The oldest persons in generation 2 reached a maximal age 89 years by 2021. Persons born after 1932 with missing links to parents were excluded. The numbers of diagnosed PCs were about 188,000 in generation 1, 127,000 on generation 2, and 3200 in generation 3.

All familial risks were calculated to men in generation when their FDR or SDR was also diagnosed with PC. The affected relatives are called **proband**s.

Familial relative risks were calculated as standardized incidence ratios (SIRs), which are the ratio of the observed number of PCs in population at risk to the expected number of PCs based on reference rates of PC. The reference population for all SIR estimates were the Swedish population of men whose FDR and SDR (grandfather, uncle) were not diagnosed with PC. The follow-up was started on the date of birth or beginning of the study (1st January 1961), whichever came later. The follow-up was terminated at death, emigration, PC diagnosis or end of study (29th December 2021), whichever came earliest. The rates were standardized based on age (5-year groups), calendar period (5-year groups), educational level (<9 years, 9 years, 10-11 years, 12 years, college <3 years, university graduate, postgraduate) and geographic region

(north, south and 3 largest cities). The 95% confidence intervals (CIs) were calculated assuming that observed rates follow Poisson distribution.

The cumulative incidence of PC was calculated non-parametrically considering death as a competing risk. Follow-up started at birth and was terminated at PC diagnosis, death, emigration or end of study.

All statistical analyses and data visualization were done using SAS and R (version 4.4.2).

## RESULTS

### Population and demographic changes between 1960 and 2023

In **Supplementary Table 1** we show the population characteristics of the Swedish data used in the study. The population consists of three generations, the earliest, generation 1 was born any time before year 1932 (median birth year 1913). From 1932 on generation 2 was born (median birth year 1949) and their children constituted generation 3 (median birth year 1979). Numbers of males and diagnosed PCs were dominated by generation 1. The median diagnostic age was 9 years higher in generation 1 compared to generation 2; it was only 54 years in generation 3.

Demographic changes have been large in PC. According to the NORDCAN database case numbers in Sweden in year 1960 were 1477 and in 2023 they were 11,338. In years 1960-64 the age maximum of cases was at 83 years, 50% of the cases were reached by 74 years and 5.9% of cases were diagnosed before age 60 years. The same measures in 2023 were 77 years, 71 years and 13.1%. In all male cancer the median diagnostic age remained at 73 from 1960 to 2023 but the proportion of cases diagnosed before age 60 years decline from 26.3% to 15.9%

Family size distribution has also changed in Sweden from 1940 (population 6.4 million) to 2000 (population 8.9 million). Families with 1 son had increased from 230,000 to 270,000, families with 2 sons had modestly increased from 100,000 to 114,000, but 3-son families had decreased from 30,000 to 25,000, and 4-or more son families decreased from 2900 to 1200. Thus, the likelihood of two brothers being diagnosed with PC has decreased.

### Familial risks transmitted from different probands

In this relatively young case population FDRs are fewer but with higher familial risks than SDRs as shown in **Fig. 1** which is drawn into the proportion of case numbers (x-axis) and SIR (y-axis). Risks between brothers reach SIR of 4.0; that for sons of father proband reaches 3.1 and that transmitted from SDR probands (uncles and grandfathers) about 1.5.

In **Fig. 2**, SIRs are shown for men in generation 3 when their fathers and maternal/paternal uncles were considered as probands (details are shown in **Supplementary Table 2**). SIRs were higher, 1.81 for maternal compared to paternal uncle proband of 1.52, which was also true for SIRs transmitted from two maternal (2.35) compared to two paternal uncles (1.89). It was even true when a father was additionally affected including two uncles (maternal 9.00 vs. paternal 5.78). If men had one affected maternal and paternal uncle (without affected father) SIR was 2.13 and it was 8.54 with an affected father (**Supplementary Table 2**).

Relative risks for PC in generation 3 men are shown in **Fig. 3** by fathers and maternal and paternal grandparents. The SIRs transmitted from maternal (1.58, N 203) and paternal (1.60, N 184) grandfathers were equal (as were also case numbers); when both grandfathers were affected the SIR was 1.75. When fathers were additionally affected the SIRs were 5.35 and 6.63, respectively. The highest SIR of 8.15 was recorded for father and both grandfather probands (N 27).

### Risks associated with different family constellations

Many men in generation 3 had multiple affected relatives (**Table 1**). The above figures showed that SIRs to generation 3 men were about equal irrespective of the type of SDR probands. We thus combined all grandfather and uncle probands. SIR for affected brothers was 4.04 and it increased to 10.3 or 13.0 when one or two SDRs were affected. When his father was affected SIR was 3.12 (N 492) and it increased stepwise to 4.68, 6.63, 8.74 and 11.6 when increasing numbers of SDRs were affected. When affected brother pairs had an affected father, SIR was 12.3 and it increased to 14.1 and 27.1 when, additionally, one or two SDRs were affected. The highest numbers of affected families were noted for an affected man in generation 3 to have one affected SDR; SIR was 1.41 but it increased to 2.56 when he had 3 affected SDRs. In **Table 1** we have marked some entities with highest numbers of familial cases, 533 with an affected father and any affected SDRs, or 713 with SDRs but no FDRs.

### Cumulative incidence

In **Fig. 4** we have plotted cumulative incidence to be diagnosed with PC by age up to 60 years. The bottom graph shows the incidence for men in the third generation without affected fathers or SDR. Just on top of this graph runs curves for those with one or two SDRs diagnosed with PC. The curve for men with affected fathers reached a cumulative incidence of 0.04 and for those with affected fathers and 2 SDRs of 0.08.

## DISCUSSION

PC has been a disease of elderly men with hugely increasing case numbers and incidence, particularly into the PSA era, coupled with some changing demographic features. The median diagnostic age in Swedish men shifted from 74 to 71 years (between 1960 and 2023) and cases diagnosed before age 60 increased from 5.9% to 13.5%. These changes have markedly influenced familial presentation of PC. The vast numbers of patients from the 1990s onwards had few fathers diagnosed with PC as this cancer was rarer earlier. In one of our first studies of familial

PC for which cases were overwhelmingly from the pre-PSA era, 15.3% of affected sons has an affected father among a total of 569 familial PCs (23). In a later study covering cancers to the end of 2006 and almost 10 times as many familial PCs, only 13.6% of affected sons had an affected father (24). In the last study covering cancer to the end of 2016 and including 24,000 familial PCs, 12.9% of affected sons had an affected father but the proportion of affected brothers had vastly increased (1). We showed above that during the course of this study the Swedish population had increased 1.4-fold but families with 3 or more sons had markedly decreased. Thus, familial counseling needs to pay increasing attention to SDRs, grandfathers and uncles. In the present relatively young generation 3 population, affected brothers were rare, affected fathers were more numerous but affected SDRs were the largest group of affected relatives.

Because of the young generation 3 familial risks between brothers (4.0) and for sons of affected fathers (3.1), in line with a previous study PC data on father and son age groups: hazard ratios of 4.9 (50-9 y vs <60 y), 4.1 (60-9 y vs <60 y) and 3.0 (70-9 y vs. <60 y) (25) Biologically, the difference between parent-offspring and sibling-sibling inheritance patterns could be that recessive effects may only be transmitted between siblings. In PC recessive effects may be weak as we also confirm here through equal familial SIRs transmitted through grandparents (maternal 1.81, paternal 1.52) and uncles (maternal 1.58, paternal 1.60), in agreement with the Utah data (20). Some studies have reported higher familial risk between brothers than father-son pairs which may be related to uneven age-adjustment or bias between brother pairs (1). There is clear evidence on bias among brotherships; when the first brother is diagnosed with PC the others seek medical care and may be diagnosed with early-onset PC (21, 26). Relating to the above comparison of risks transmitted through maternal and paternal relatives, autosomal inheritance would not show sex distinctions and genetic counselors would require family data from both lineages. Yet many patients may wonder how their mothers could influence their PC.

Familial risk typically increases at early age and if several family members have been diagnosed with the same cancer. For example in the literature, when two or more FDRs were diagnosed with PC familial SIR increased to 3.74 compared to 2.20 with one FDR affected (1). We have shown even much higher familial risks of 8.51 when father and two brothers were probands or of 17.74 when three brothers were probands (27). In the current database the oldest diagnosed men in generation 3 were 68 years but the median age was only 54 years. Thus affected brotherships were few and they were almost all brother pairs. However, the advantages of considering 3 generations for genetic counseling are clear in **Table 1**. When a young man is diagnosed with PC and the doctor finds out that he had an affected father (SIR 3.12) he may suspect genetic risk. However, lacking other evidence, the genetic counselor would probably suggest no genetic testing. Fortunately, many young patients should be able to report on affected uncles or grandfathers, providing more information about the possible genetic risk; with 4 SDR probands SIR was 11.6. The highest SIR of 27.1 was found for families with cases in 3 generations.

The present kind of data would allow testing of interactions between risks of relatives. We observed superficially that many of the risks appear to be multiplicative which is commonly found for risk factors (**Table 1**) (28). As an apparent deviation, SIR for a man in generation 3 was 1.41 when he had only a SDR proband. SIR for brother pairs (without other probands) was 4.04. When affected brother pairs also had a SDR proband SIR was 10.3 which was more than

multiplicative risk of 5.7. Similarly, when affected brothers pairs had two SDR probands SIR was 13.0, higher than multiplicative risk of 8.2 ( $4.04 \times 2.04$ ). Case numbers are too few to provide significant results.

The basic limitation of this study is the relatively young age of generation 3 men and hence low case numbers of PCs between brothers. However, excluding the Icelandic and Utah genealogic databases, we are not aware of a setting where studies on PC in three generations could be conducted with a statistical power anyway close to the present one.

In conclusion, multigenerational family studies on PC have so far limited statistical power because the PSA-related vast increase in case numbers affected essentially one generation of men whose fathers were rarely affected but whose sons are now entering risk age. These changes took place on top of slowly decreasing family sizes and hence decreasing numbers of FDRs. We show here that for the young patients in generation 3 the richest sources of familial cases are SDRs. Uncles belong to the generation of fathers, and they are likely to be more numerous than grandparents. The results show that for genetic counseling of PC both maternal and paternal lineages should be used as they provide equal information about the familial risk of PC.

## FIGURE LEGENDS

**Fig. 1.** Familial risk (SIR) for PC in men in generation 3 according to the type of proband in x-axis which is drawn in proportion to the case numbers. Familial risk is calculated for men with a single proband.

**Fig. 2.** Familial risk (SIR) for PC in men in generation 3 according to numbers of father and uncle probands. The defined probands do not exclude other rare probands in the considered families.

**Fig. 3.** Familial risk (SIR) for PC in men in generation 3 when their fathers and/or grandfathers (GF) were probands. The defined probands do not exclude other rare probands in the considered families.

**Fig. 4.** Cumulative incidence of PC by age 60 years for men in generation 3 when their defined relatives were probands.

## ADDITIONAL INFORMATION

### Data availability

Anyone wishing to use these data should contact the National Board of Health and Welfare, Stockholm.

### Ethics

The study was approved by the Regional Ethical Review Board in Lund University, February 6, 2013 (Reference 2012/795 and subsequent amendments). Informed consent is by law not needed for use of national register data. The study was conducted in accordance to Declaration of Helsinki.

#### Author contributions

Design: KH, OH

Acquisition of data: KS, JS.

Statistical analysis and interpretation: FZ, KH, AF, AH

Manuscript writing: KH and all other authors.

Approval of the final text: All authors

#### CONFLICT OF INTEREST

A.H. is shareholder in Circio Holdings ASA. A.H. is employee and shareholder in TILT Biotherapeutics Ltd. Other authors declared no conflict of interest.

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#### Competing financial interests

A.H. is shareholder in Circio Holdings ASA and employee and shareholder in TILT Biotherapeutics Ltd. Other authors declared no conflict of interest.

#### Consent for publication

Own data were used.

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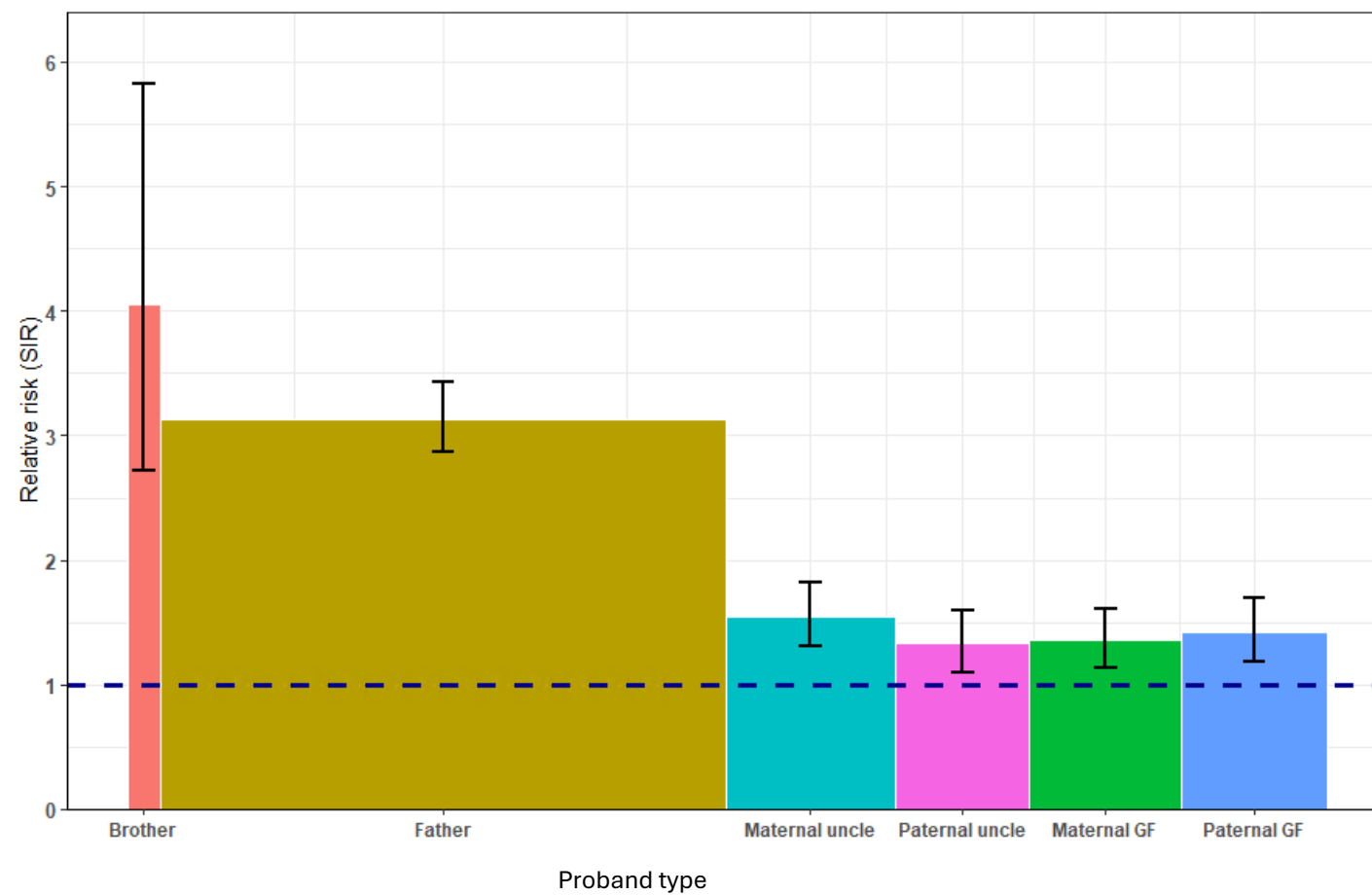
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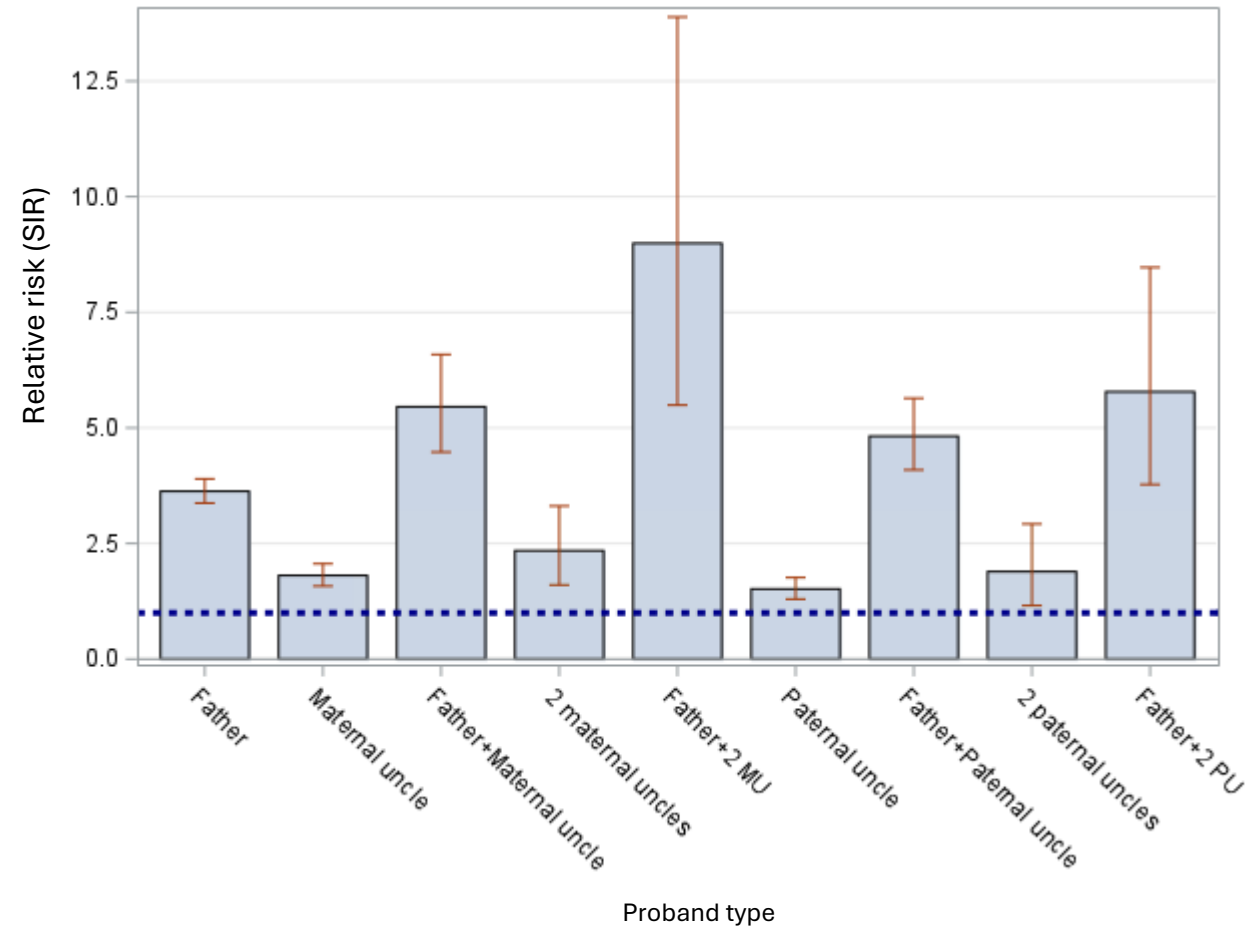
**Table 1.** Case numbers and relative risks for prostate cancer in generation 3 men according to the types and numbers of probands (brothers, fathers and second-degree relative, SDRs).

| Probands diagnosed with PC | N cases |     | SIR [95% CI]      |
|----------------------------|---------|-----|-------------------|
| Brother + 0 SDR            |         | 29  | 4.04 [2.71-5.80]  |
| Brother + 1 SDR            |         | 31  | 10.3 [6.98-14.60] |
| Brother + 2 SDR            |         | 9   | 13.0 [5.97-24.80] |
| Father + 0 SDR             |         | 492 | 3.12 [2.85-3.41]  |
| Father + 1 SDR             | 533     | 347 | 4.68 [4.20-5.20]  |
| Father + 2 SDR             |         | 134 | 6.63 [5.56-7.86]  |
| Father + 3 SDR             |         | 41  | 8.74 [6.27-11.9]  |
| Father + 4 SDR             |         | 11  | 11.6 [5.80-20.8]  |
| Brother + father + 0 SDR   |         | 39  | 12.3 [8.78-16.9]  |
| Brother + father + 1 SDR   |         | 26  | 14.1 [9.22-20.70] |
| Brother + father + 2 SDR   |         | 18  | 27.1 [16.1-42.90] |
| 1 SDR, no FDR              | 713     | 523 | 1.41 [1.29-1.54]  |
| 2 SDR, no FDR              |         | 153 | 2.04 [1.73-2.39]  |
| 3 SDR, no FDR              |         | 37  | 2.56 [1.81-3.53]  |

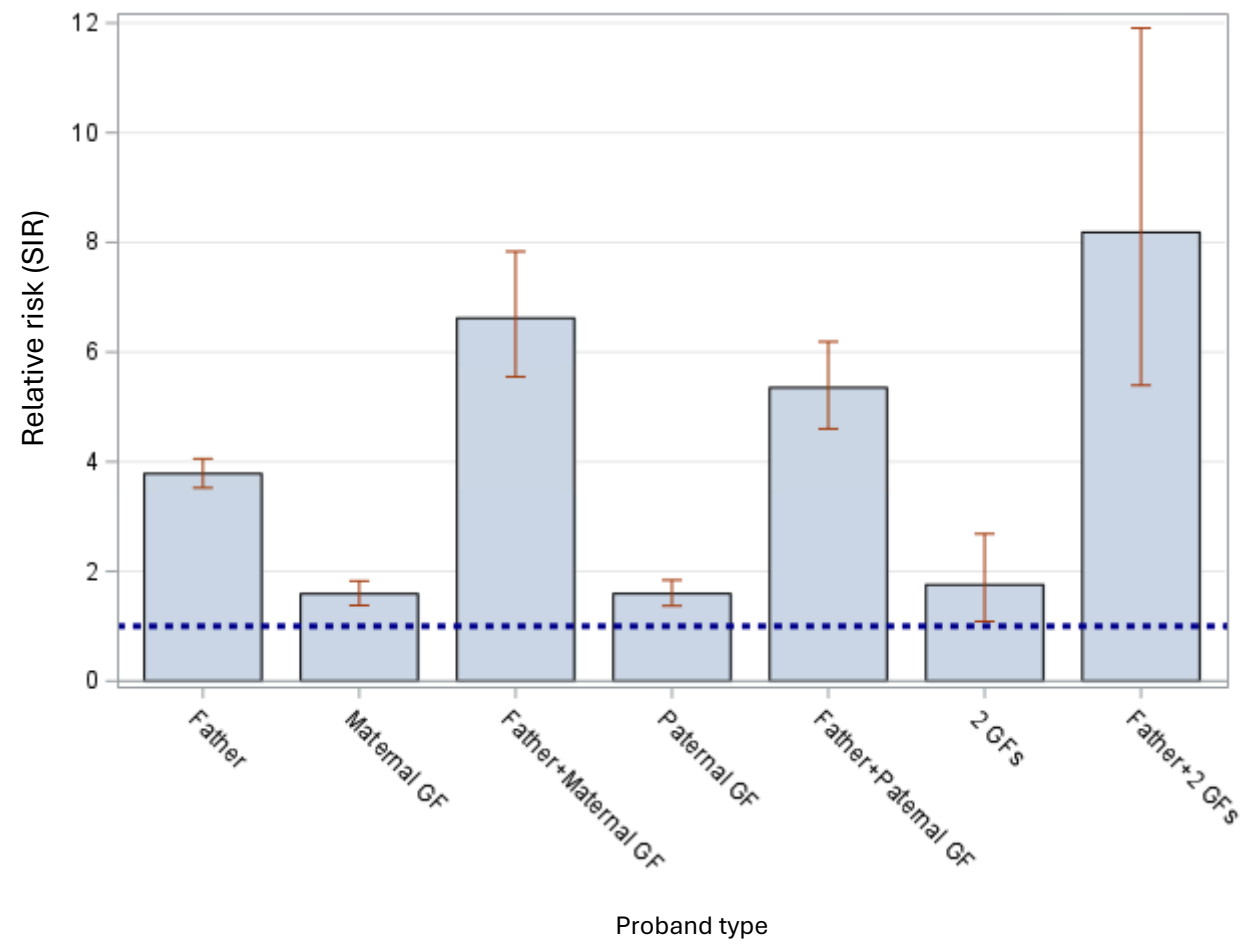
**Fig. 1**



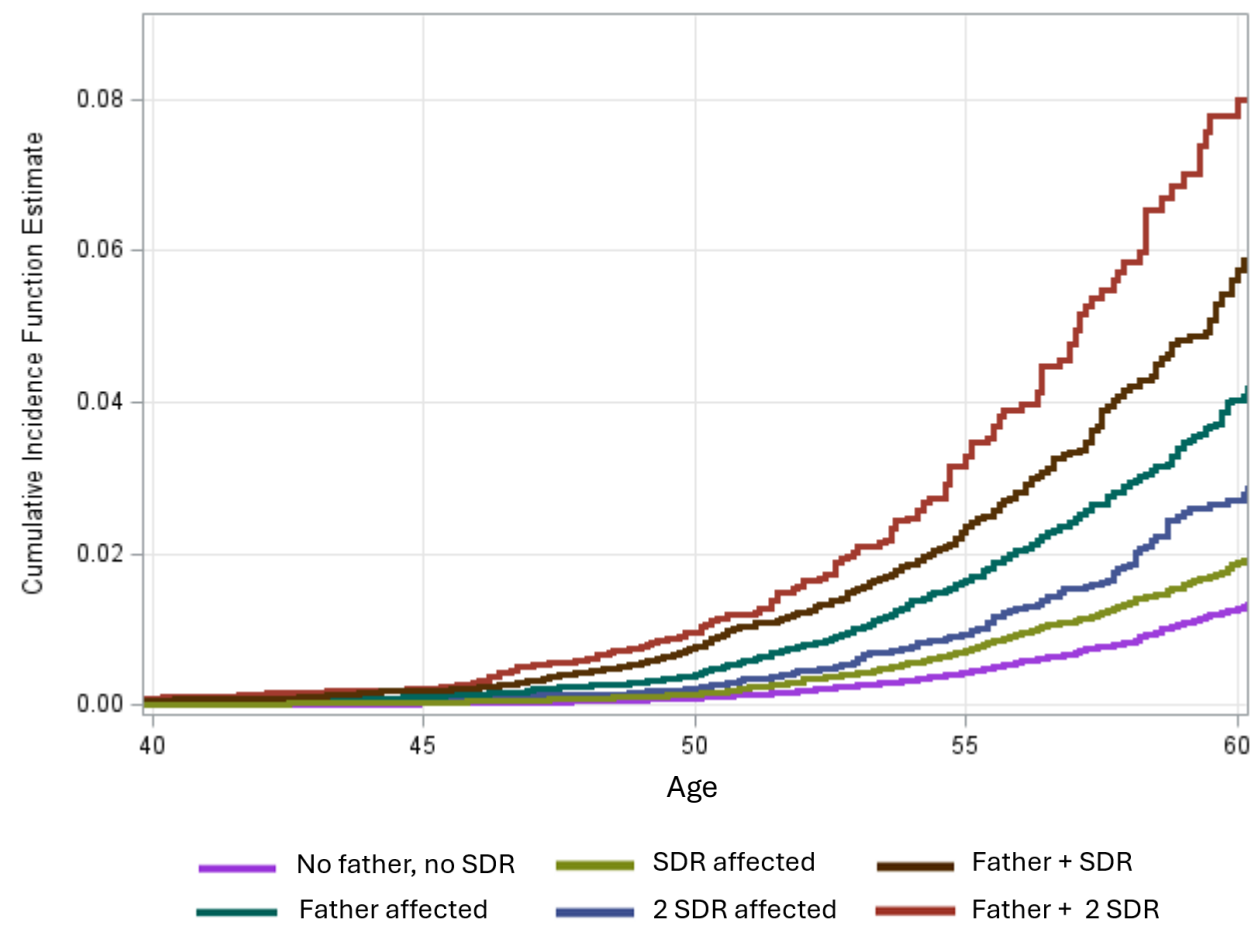
**Fig. 2**



**Fig. 3**



**Fig. 4**



**Supplementary Table 1.** Relative risk for PC based on presence of PC in father and uncles. Families with other type of affected proband are not excluded from analysis.

| Generation | Year of birth<br>median [min<br>max] | Total males | PC cases | Diagnostic age<br>median [min<br>max] |
|------------|--------------------------------------|-------------|----------|---------------------------------------|
| 1st        | 1913 [1865 1931]                     | 1 985 583   | 188 767  | 76 [38 104]                           |
| 2nd        | 1949 [1932 2006]                     | 1 371 590   | 127 024  | 67 [16 89]                            |
| 3rd        | 1976 [1949 2021]                     | 1 330 724   | 3 207    | 54 [21 68]                            |

**Supplementary Table 2.** Relative risk for PC based on presence of PC in father and uncles. Families with other type of affected proband are not excluded from analysis.

| Number of probands with PC |                 | Father | N cases | SIR [95% CI]       |
|----------------------------|-----------------|--------|---------|--------------------|
| Maternal uncles            | Paternal uncles |        |         |                    |
| 0                          | 0               | 1      | 752     | 3.63 [3.37-3.9]    |
| 0                          | 1               | 0      | 171     | 1.52 [1.3-1.76]    |
| 0                          | 1               | 1      | 155     | 4.82 [4.09-5.64]   |
| 0                          | 2               | 0      | 20      | 1.89 [1.15-2.92]   |
| 0                          | 2               | 1      | 26      | 5.78 [3.78-8.47]   |
| 0                          | 3               | 1      | 5       | 5.22 [1.7-12.19]   |
| 0                          | 4               | 1      | 3       | 12.6 [2.59-36.7]   |
| 0                          | 5               | 1      | 1       | 7.51 [0.19-41.9]   |
| 1                          | 0               | 0      | 223     | 1.81 [1.58-2.06]   |
| 1                          | 0               | 1      | 108     | 5.46 [4.48-6.59]   |
| 1                          | 1               | 0      | 24      | 2.22 [1.42-3.3]    |
| 1                          | 1               | 1      | 32      | 8.78 [6.01-12.4]   |
| 1                          | 2               | 0      | 1       | 0.91 [0.02-5.08]   |
| 1                          | 2               | 1      | 6       | 11.43 [4.2-24.89]  |
| 1                          | 3               | 0      | 2       | 15.8 [1.92-57.1]   |
| 1                          | 3               | 1      | 1       | 13.4 [0.34-74.5]   |
| 2                          | 0               | 0      | 32      | 2.35 [1.61-3.31]   |
| 2                          | 0               | 1      | 20      | 9 [5.5-13.9]       |
| 2                          | 1               | 0      | 8       | 5.77 [2.49-11.4]   |
| 2                          | 1               | 1      | 4       | 11.01 [3-28.2]     |
| 2                          | 2               | 1      | 1       | 15.6 [0.40-87.1]   |
| 3                          | 0               | 0      | 6       | 3.82 [1.4-8.32]    |
| 3                          | 0               | 1      | 1       | 4.44 [0.11-24.75]  |
| 3                          | 1               | 0      | 1       | 4.66 [0.12-26.0]   |
| 3                          | 1               | 1      | 1       | 29.02 [0.73-161.7] |
| 4                          | 0               | 0      | 2       | 10.1 [1.23-36.6]   |
| 6                          | 3               | 1      | 1       | 60.4 [1.53-336.7]  |